Lilly

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Ln., Rm. 1061
Rockville, MD 20852

Re: [Docket No. 98D-0994] Guidance for Industry; BACPAC I
Federal Register: November 30, 1998 (Volume 63, Number 229)

Dear Madam or Sir:

Eli Lilly and Company are pleased to have the opportunity to provide comments on the draft guidance for industry, BACPAC I: Intermediates in Drug Substance Synthesis.

We commend the FDA for producing a document which provides a scientifically based approach to making post approval changes to synthetic intermediates while lessening the regulatory reporting burden. Attached please find our comments on the draft guidance. We hope that these comments will result in revisions that further enhance the positive impact of this guidance.

Please feel free to contact me at (317) 276-0368 for clarification of any comments.

Sincerely,

Tobias Massa, Ph.D.
Director, Global Regulatory Affairs
Chemistry Manufacturing and Control

cc: Dr. D. Miner

Attachment

98D-0994

C14

Eli Lilly and Co. Comments on BACPAC I 3/25/99

Re: "Guidance for Industry. BACPAC I: Intermediates in Drug Substance Synthesis. Bulk Actives Postapproval Changes: Chemistry, Manufacturing and Controls Documentation."

Eli Lilly and Company applauds the efforts which the FDA has expended to develop the BACPAC-I draft guidance document. This document represents a significant improvement of the process by which important drug substance manufacturing changes may be understood, validated, implemented by Industry and appropriately reported to the Agency. We also appreciate the opportunity to comment on the document.

We have divided our comments into three classes:

- comments which apply to several places in the document
- single issue-related comments
- specific suggested wording improvements

I. General comments

A. Historical Data: We support the proposal of the Agency to base comparisons on data from 10 representative batches and to apply the statistical approach of mean plus three standard deviations to choosing limits for these comparisons. This provides a very sound approach for the majority of situations.

However, we would make two suggestions for improvement. First, the guidance should allow inclusion of more than 10 batches where available. Secondly, we believe that situations where less than 10 relevant batches are available will not be a rare event and that in most cases the same approach of using the mean plus three times the standard deviation should apply. (As the number of premodification batches decreases there is an increased likelihood that truly equivalent materials would test as non-equivalent but in such cases the sponsor would always to able to move to evaluating equivalence at the next isolated intermediate). So consistent with the earlier comment regarding consulting of the review division, we would suggest the following revised texts:

Line 124 ....data from ten **or more** premodification commercial batches **if available.**
Line 589 ...from 10 **or more** recent batches representative of the established process **if available**.

Lines 591-593 (~~The appropriate review division(s) should be contacted for concurrence in those rare instances~~ .....~~<10 batches.~~) **In cases where <10 commercial batches are available for use as historical comparators (e.g., low-volume drug substances) as many pilot scale batches as are appropriate should be included as comparators. In all cases a minimum of three total premodification batches are required.**

B. Documentation package:

- BACPAC-I includes in multiple places the proposed submission of validation data for new test methods (lines 120, 243, 289, 333, 346, 375, 417, 456, and 511). This has the potential of substantially increasing the regulatory reporting burden both on industry and on the FDA. It has not been common practice to include the details of methods for raw materials and intermediates in NDAs, much less validation data for those methods. Thus we would request that the Agency modify the BACPAC-I requirements in accordance with current practice. In keeping with current regulatory responsibilities, Office of Regulatory Affairs inspectors are able to request and review the complete validation data set. We believe that this position is absolutely necessary to reduce the volume of information and the ensuing review burden on FDA reviewers. An example of the proposed change follows for lines 120-1.

  When new methods are developed for this purpose, ~~validation data should be provided~~ ***they should be validated and the data should be available for inspection****.*

- Certificates of Analysis are requested for the documentation package to support most changes. In the case of changes to site, scale and process (lines 259, 305, 439 and 477) this request is limited to COAs for outsourced intermediates affected by the proposed change. We would suggest the following addition to the wording:

  A Certificate of Analysis ***or batch release data*** *from the supplier for each outsourced intermediate affected by the change*

However in the case of spec changes (line 349-50 and 391-2) the request is broadened to include raw materials and solvents. Given that BACPAC-I applies only to early intermediates, the risk of problems occurring from spec changes to raw materials and solvents is very low. Thus, providing COAs for these materials would represent an unnecessary reporting burden. Therefore we would propose only including data which demonstrates that any intermediates meet appropriate specifications established for the material. These sections should read for line 349-50 for example:

A Certificate of Analysis ***or batch release data*** *from the supplier for each outsourced intermediate affected by the change*

II. Item specific comments

A. Changes to the impurity profile of an intermediate (reference lines 132 through 136). It is not clear from the wording of this section that the requirement to limit a new impurity in an intermediate to 0.1% is a sufficient but not a necessary result to establish the absence of new impurities. ICH Q1A provides the 0.1% limit as a toxicological limit established for the purposes of evaluating impurities in the final drug substance (not intermediates). It is presumed that BACPAC-I has included the same limit for intermediates since the lack of new impurities greater than 0.1% in an intermediate would certainly guarantee the absence of significant new impurities in the final drug substance. However, we would propose to add a citation to the earlier section (lines 105-117) where BACPAC-I clarifies what steps may be taken the event of a new impurity being seen above the threshold limit of 0.1% in an intermediate. Also, we would strike the latter two sentences of 1.a. (lines 133-136) since the first sentence could be misread to imply that the ICH limit applies to intermediates and the second is well known. As proposed, this section would read:

1. An intermediate:

a. No new impurity is observed at or above 0.1 percent. ***In cases where new impurities are observed in the intermediate above 0.1 %, as defined in Section III. A., the applicant may evaluate subsequent intermediates or the final drug substance to confirm levels do not exceed the 0.1 % threshold.*** ~~*This impurity level is judged to be appropriate for intermediates leading to either low-dose or high-dose drugs. Further reduction of impurity levels will frequently occur in the subsequent step or steps prior to drug substance formation.*~~

B. In lines 137-140 provision should be made for those cases where limits have been previously registered. The text would read as follows:

a. Existing impurities, including residual organic solvents, are ***within the stated limits or, if not previously specified, are*** at or below the upper statistical limit of historical data.

b. ~~***Total impurities*** are at or below the upper statistical limit of historical data.~~ ***Total impurities are within the stated limits or, if not previously specified, are at or below the upper statistical limit.***

C. Site changes (lines 205-272): The designation of most site changes as being appropriate for inclusion in an annual report is consistent with FDAMA. However, the documentation suggested for inclusion in the annual report represents an unneeded regulatory burden. Where a

manufacturer is moving a manufacturing process to a different site but where (1) the new facility has been operating in compliance with cGMPs and (2) there are no changes in the chemistry, control strategy, analytical methods, reagents, etc. a notification in the annual report should suffice. Detailed information supporting such changes should more appropriately be maintained by the manufacturer and available for inspection.

D. We would suggest that the "site change" referred to in lines 270-272 be annual reportable. Given the clear criteria for making comparisons laid out in this draft guidance, filing a supplement for a site change in cases where the new site is owned by a contract manufacturer already approved for the same application seems quite unnecessary.

E. Due to the broad range of changes which are covered under section IV.C.1., "Manufacturing Process Changes - Changes that do not involve new starting materials or Intermediates" (lines 399-442), we propose that this section include a category of "Annual Report" items in addition to those requiring a "Changes Being Effected" supplement. Rather than attempting to provide line items corrections, we have provided a replacement section for lines 399-442.

1. *Changes That Do Not Involve New Starting Materials or Intermediates*

   a. Changes in solvents or reagents

   Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

   ·*Description of change.*

   ·*Specification(s) for new reagents and solvents ~~and Certificates of Analysis from the suppliers, if applicable.~~*

   ·*Evaluation of the impurity profile and physical properties:*

   A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made using material produced by the changed process, historical data for comparison, and a description of the source of the historical data. A summary of validation studies should be provided to the submission and validation data should be ***generated and made available for inspection*** *for new test methods and also for existing methods if their use is being extended beyond their original purpose.*

If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

When a new solvent is introduced into the synthetic process, the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established as appropriate. The level of the new solvent in the drug substance should be below its ICH Q3C Option 1 limit. If the level of the new solvent in an intermediate is at or below the ICH Q3C Option 1, no testing of the drug substance is needed.

*If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, the change should not be implemented until a supplement for the modification has been approved. When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) ~~should~~ **may** be contacted for guidance.*

- *A Certificate of Analysis from the supplier **or batch release data** for each outsourced intermediate affected by the process change.*

Filing Documentation:

- *Changes being effected supplement.*

b. Changing in-process parameters (e.g. temperature, pH, stoichiometry, time); or repeating a purification step already in the application

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report to the application(s), as appropriate):

- *Description of change.*

- *Evaluation of the impurity profile and physical properties:*

A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made using material produced by the changed process, historical

data for comparison, and a description of the source of the historical data. A summary of validation studies should be provided to the submission and validation data should be ***generated and made available for inspection*** *for new test methods and also for existing methods if their use is being extended beyond their original purpose.*

If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, the change should not be implemented until a supplement for the modification has been approved. When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) may be contacted for guidance.

- *A Certificate of Analysis from the supplier* ***or batch release data*** *for each outsourced intermediate affected by the process change.*

Filing Documentation:

- ***Annual Report***

F. Because no attempt is made to classify scale changes (lines 275, 276) this section could be interpreted that all changes no matter how minor need to be reported in the annual report. We would suggest inclusion of a minimum factor (e.g. 5X) below which changes need not be reported.

III. Suggested wording improvements

Line 95 ....if the drug substance is a mixture of isomers **and the change(s) potentially affects the relative abundance of the isomers, then data to verify** the same quantitative mixture should be .....

Line 188 Consequently, **in the unusual case where minor changes in the impurity profile affect** physical properties of the drug substance **which** ~~when they~~ are relevant to the finished dosage form performance, **the physical properties** should be evaluated unless equivalence....

Line 582 ...must include covalent bond formation **and/or cleavage**;